REMARKS

Rejection of the claims under 35 USC 103:

Claims 5, 7, 8, and 21 have been rejected under 35 U.S.C. 103(a) as being anticipated by Adams et al. (US 2005/0153926) in view of Heller et al. (Journal of Applied Polymer Science, Vol. 22, p. 1991-2009, 1978).

Claims 12, 16, 17, and 22 have been rejected under 35 U.S.C. 103(a) as being anticipated by Adams et al. in view of Heller et al. and Tonge et al. (U.S. Patent 6,436,905).

Applicants have amended the claims to obviate the rejection. Support for the amendments can be found in the specification on page 3 lines 9-11, page 4 line 29 to page 5 line 6, and page 6 lines 7-21.

Adams et al. teach a method of attaching a nucleic acid to a polymer. Adams et al. further teach "The polymers of the invention can have substantially any structure achievable by using subunits having a polymerizable or otherwise reactive ethylene moiety." [0041]. Finally, Adams et al. teach "It is understood that the present invention is intended to encompass all types of frameworks capable of presenting functional groups that are reactive towards the ethylene-containing moiety of the subunits." [0065]. Thus Adams effectively teaches that *any* polymer modified in *any* way is suitable for combination with their modified nucleic acid. Adams et al. do not provide any teaching of any membrane active polyanion, nor provide any motivation for the desirability of any membrane active polyanion. Therefore, starting from Adams et al. one skilled in the art would not be motivated to make any membrane active polyanion nor search the art for any membrane active polyanion.

Applicants note that while Adams et al. teach that a hydrophobic group may be added to the polymer [0050-0052], one of ordinary skill in the art will readily recognize that the simple addition of any hydrophobic group to any polymer does not create membrane active polyanion. Applicants' amendment to the claims makes it clear that sufficient hydrophobic modification is performed to give the polymer the desired characteristic. Specifically, Applicants have amended the claims to recite increasing hydrophobicity of the copolymer by randomly attaching hydrophobic groups along the copolymer backbone in a sufficient amount to form a membrane active polyanion capable of lysing mammalian cell membranes at pH 6.5.

Applicants acknowledge that Adams et al. teach "the physicochemical characteristics (e.g., hydrophobicity, hydrophilicity, surface activity, conformation) of the polymer are altered by attaching a monovalent moiety which is different in composition than the constituents of the bulk polymer and which does not bear a nucleic acid." [0057]. However, again, one of ordinary skill in the art will readily recognize that *any* modification of *any* polymer will alter the physicochemical characteristics of the polymer. It is the Applicants' opinion that this teaching encompasses every conceivable modification without limit and does not teach or provide motivation for any particular desirable physicochemical characteristic. Nor does this teaching providing any direction for making of membrane active polymer in particular nor of the desirability of doing so.

The Action states that it would have been obvious to one of ordinary skill in the art at the time of the invention, to modify the method of delivering a polynucleotide to the cytoplasm of a cell of Adams et al. to include the addition of a single hydrophobic group to a maleic acid anhydride moiety at taught by Heller et al. because Adams et al. taught a) reacting polymers with hydrophobic groups and b) the desirability of a water-soluble polymer. It is the position of the Action that Heller et al. teaches providing a carboxylic acid group and a hydrophobic group maintains water solubility. Applicants respectfully disagree. First, it is the Applicants' opinion that the teaching of Adams et al., water-soluble polymers including those modified with hydrophobic groups, encompasses an infinite number of polymers with infinite physicochemical characteristics, and contains no teaching or direction to one of skill in the art as to the benefit of a membrane active polyanion. Second, Heller et al. teach that their polymers, containing hydrophobic groups and carboxylic acid groups, are useful for delivering drugs (nucleic acids) by the initially associating the drug with the insoluble (protonated) polymer, which them releases the drug as in becomes solubilized (deprotonated).

Heller teaches a means to start with a water-*insoluble* polymer which is slowly solubilized. "In this case, side-group reaction might be the rapid process that leads to chain solubilization and hence drug release," "A more desirable approach involves the synthesis of hydrophobic, water-*insoluble* polymers that can release a drug by erosion *(solubilization)* of the matrix but from which only a minimal amount of the drug is released by a diffusion process." (page 1992). "Since in all experiments depletion of drug also coincided with total polymer dissolution, it can again be assumed that drug release and polymer erosion occur

concomitantly." (page 1999). Heller et al. explicitly teach, that the usefulness of their polymers lies in the polymer having both soluble and insoluble states and that the drug (nucleic acid) is associated with the polymer in the *in*soluble state. Therefore, one would not have been motivated to combine the teachings of Heller et al. and Adams et al., since Adams et al. solely requires that the polymer be water-soluble.

Applicants further note that in both Takeda v. Alphapharm and Eisai Co. Ltd. V. Dr. Reddy's Laboratories, the courts have found that there must be motivation in the prior art to select a lead compound (in the instant case a styrene-maleic anhydride random copolymer or butyl vinyl ether-maleic anhydride alternating copolymer). The courts have further found that a finite number of identified, predictable solutions is critical to obviousness and turns on the evidence available to a person of skill when the invention was made. Adams et al. lists a large abundance of potential water soluble polymer backbones with no suggestion that modification of a styrene-maleic anhydride random copolymer or butyl vinyl ether-maleic anhydride alternating copolymer is a particularly useful. Nor does Adams et al. suggest any specific modification of a styrene-maleic anhydride random copolymer or butyl vinyl ether-maleic anhydride alternating copolymer. Adams et al. only teach that polymers may be modified in any way. Finally, Adams et al. provides no suggestion for modifying any polymer to render the polymer membrane active at pH 6.5. The only predictable outcome of combining the polymers taught by Heller et al. with the method taught by Adams et al. is that, under certain circumstances, the polymers taught by Heller will be water soluble.

In light of their remarks, Applicants request reconsideration of the rejections.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 5, 7, 8, 12, 16-17 and 21-22 should be allowable.

Respectfully submitted,

/Kirk Ekena/

Kirk Ekena Reg. No. 56,672
Roche Madison Inc.
505 South Rosa Road
Madison, WI 53719
608-238-4400

I hereby certify that this correspondence is being transmitted to the USPTO on this date: 07/07/2009 .

/Kirk Ekena/
Kirk Ekena